

AMENDMENTS TO THE SPECIFICATION

Please replace all paragraphs found on Page 10 with the following rewritten paragraphs:

PCN 2/24/04
A-E
Figure 1_A depicts a nucleic acid sequence (SEQ ID NO:1) encoding human glial cell line-derived neurotrophic factor receptor ~~(GDNFR-α)~~ (GDNFR-α; SEQ ID NO:2). The amino acid sequence of the full length GDNFR protein is encoded by nucleic acids 540 to 1934 of SEQ ID NO:1.

Figure 2 depicts the amino acid sequence (SEQ ID NO:2) of the full length human GDNFR-α protein.

PCN
A-D
Figure 3_A depicts a nucleic acid sequence (SEQ ID NO:3) encoding rat GDNFR-α (SEQ ID NO:4). The amino acid sequence of the full length GDNFR-α protein is encoded by nucleic acids 302 to 1705 of SEQ ID NO:3.

Figure 4 depicts the amino acid sequence (SEQ ID NO:4) of the full length rat GDNFR-α protein

Figure 5 (A) – (K) depicts the alignment and comparison of portions of GDNFR-α cDNA sequences (SEQ ID NOS:46-55) produced in various clones as well as the consensus sequence for human GDNFR-α (SEQ ID NO:45).

Figure 6 depicts the identification of Neuro-2A derived cell lines expressing GDNFR-α.

Figure 7A and 7B depict the results of the equilibrium binding of [¹²⁵I]GDNF to cells expressing GDNFR-α.

Please replace the paragraphs beginning on page 11, lines 33, and ending on page 12 line 1, with the following rewritten paragraphs:

PCN
A-D
Figure 18_A depicts the alignment and comparison of various human, rat and mouse GDNFR amino acid sequences (SEQ ID NOS:2, 4, and 56, respectively).

PCN
A-C
Figure 19 depicts the alignment and comparison of human GDNFR-α, rat, and mouse GDNFR-α, human GRR2, rat GRR2 AND human GRR3 and rat GRR3 amino acid sequences ((SEQ ID NOS:2, 4, 36, 40, 38, and 42, respectively) and an exemplary consensus GDNFR sequence (SEQ ID NO:43).

POLYNUCLEOTIDES ENCODING GDNF RECEPTOR- α -RELATED
NEUROTROPHIC FACTOR RECEPTORS PROTEIN 3

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1. Field of the Invention

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The present invention relates to receptors for neurotrophic factors. In particular, the invention relates to receptors for glial cell line-derived neurotrophic factor (GDNF) and neurturin and provides nucleic acid and amino acid sequences encoding the receptors. The present invention also relates to therapeutic techniques for the treatment of neurotrophic factors-responsive conditions.

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2. Background of the Invention

Glial Cell line-Derived Neurotrophic Factor

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Glial cell line-derived neurotrophic factor (GDNF) was initially isolated and cloned from rat B49 cells as a potent neurotrophic factor that enhances survival of midbrain dopaminergic neurons (Lin et al., Science, 260, 1130-1132, 1993). Recent studies have indicated that this molecule exhibits a variety of other biological activities, having effects on several types of neurons from both the central and peripheral nervous systems. In the central nervous system (CNS), GDNF has been shown to prevent the axotomy-induced death of mammalian facial and spinal cord motor neurons (Li et al., Proceedings Of The National Academy Of Sciences, U.S.A., 92, 9771-9775, 1995; Oppenheim et al., Nature, 373, 344-346, 1995; Yan et al., Nature, 373, 341-344, 1995; Henderson et al., Science, 266, 1062-1064, 1994; Zurn et al., Neuroreport, 6, 113-118, 1994), and to rescue developing avian motor neurons from natural programmed cell death (Oppenheim et al., 1995 supra). Local administration of GDNF has been shown to protect nigral dopaminergic neurons from axotomy-induced (Kearns and Gash, Brain Research, 672, 104-111, 1995; Beck et al., Nature, 373, 339-341, 1995) or neurotoxin-induced degeneration (Sauer et al., Proceedings Of The National Academy Of Sciences U.S.A., 92, 8935-8939, 1995; Tomac et al., Nature, 373, 335-339, 1995). In addition, local administration of GDNF has been shown to induce sprouting from dopaminergic neurons, increase levels of dopamine, noradrenaline, and serotonin, and improve motor behavior (Tomac et al., 1995 supra).

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More recently, GDNF has been reported to be a potential trophic factor for brain noradrenergic neurons and Purkinje cells. Grafting of fibroblasts ectopically expressing GDNF prevented 6-hydroxydopamine-induced degeneration and promoted the phenotype of adult noradrenergic neurons in vivo (Arenas et al., Neuron, 15,

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